PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Dykstra et al. Group Art Unit: 1626

U.S. Patent No. 7,183,286

Serial No.: 10/796,657 Examiner: Grazier, N.

Filed: March 9, 2004 Docket No.: 421/60/18/2/2

Confirmation No.: 2624

For: COMPOUNDS, METHODS AND COMPOSITIONS USEFUL FOR THE TREATMENT OF BOVINE VIRAL DIARRHEA VIRUS (BVDV) INFECTION AND HEPATITIS C VIRUS (HCV) INFECTION

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REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTENTION: Decision and Certificate of Correction
Branch of the Patent Issue Division

Sir:

Please find attached a Certificate of Correction, Form PTO/SB/44, in connection with the above-captioned U.S. Patent No. 7,183,286.

The first three corrections are to the title page of the patent. Applicants inadvertently included an incorrect spelling for the city of residence of inventor Chad E. Stephens on the Declaration. In addition, the Patent Office included typographical errors in the names of inventors Arvind Kumar and Chad E. Stephens on the title page.

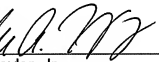
The fourth correction is to column 1 of the patent. Applicants inadvertently included an incorrect grant number in the Statement of Government Support.

It is noted that the errors that appear in this patent occurred in good faith. Correction thereof does not involve such changes in the patent as would constitute new matter or would require re-examination.

The Commissioner is hereby authorized to charge the $100.00, any deficiencies of payment, or credit any overpayment associated with the filing of this Certificate of Correction to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: 05/14/2009 By: 

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421/60/18/2/2 AAT/AWD

Enclosures

PTO/SB/44 (09-07)
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(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,183,286

APPLICATION NO. : 10/796,657

ISSUE DATE : 2/27/2007

INVENTOR(S) : Dykstra et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On title page, item 75 Inventors
replace "Arvid Kumar"
with –Arvind Kumar–.

On title page, item 75 Inventors
replace "Chad F. Stephens"
with –Chad E. Stephens–.

On title page, Item 75 Inventors
replace "Villa Roca, GA (US)"
with –Villa Rica, GA (US)–.

On column 1, line 21
replace "AI33383"
with –AI33363–.

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(12) **United States Patent**
Dykstra et al.

(10) **Patent No.: US 7,183,286 B2**
(45) **Date of Patent: Feb. 27, 2007**

(54) **COMPOUNDS, METHODS AND COMPOSITIONS USEFUL FOR THE TREATMENT OF BOVINE VIRAL DIARRHEA VIRUS (BVDV) INFECTION AND HEPATITIS C VIRUS (HCV) INFECTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/796,657**

(22) Filed: **Mar. 9, 2004**

(65) **Prior Publication Data**

US 2007/0010533 A1 Jan. 11, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/044,315, filed on Jan. 11, 2002, now abandoned.

(60) Provisional application No. 60/261,654, filed on Jan. 13, 2001.

(51) **Int. Cl.**

A61K 31/506	(2006.01)
A61K 31/4184	(2006.01)
C07D 401/14	(2006.01)
C07D 235/04	(2006.01)

(52) **U.S. Cl.** **514/269**; 514/394; 544/333; 548/304.7

(58) **Field of Classification Search** 514/269, 514/394; 544/333; 548/304.7
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to novel compounds and methods that are useful in treating members of the Flaviviridae family of viruses. Compounds of the present invention will have a structure according to Formulas (I)–(VI) as recited throughout the application.

40 Claims, 1 Drawing Sheet

COMPOUNDS, METHODS AND COMPOSITIONS USEFUL FOR THE TREATMENT OF BOVINE VIRAL DIARRHEA VIRUS (BVDV) INFECTION AND HEPATITIS C VIRUS (HCV) INFECTION

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 10/044,315, filed Jan. 11, 2002, now abandoned the disclosure of which is incorporated herein by reference in its entirety, which claims priority to U.S. Provisional Application No. 60/261,654, filed Jan. 13, 2001, the disclosure of which is incorporated herein by reference in its entirety.

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under grant number K08 AI01728-01 and U01-A133383 from the National Institutes of Health. The United States government may have certain rights in this invention.

FIELD OF THE INVENTION

This invention relates to the treatment of bovine viral diarrhea virus (BVDV) and hepatitis C virus (HCV) infections.

BACKGROUND OF THE INVENTION

Bovine viral diarrhea virus (BVDV) is an enveloped, single-stranded, positive sense RNA virus in the genus Pestivirus and the family Flaviviridae. Based on the presence or absence of visible cytopathic effect when susceptible cell monolayers are infected, two pathogenic biotypes of BVDV, referred to as cytopathic and noncytopathic, have been identified. Perdrizet J A in: B. P. Smith (ed), *Large Animal Internal Medicine, First Edition* (Mosby Press, St Louis, 731–737 (1990)). A differentiation is also made between biotypes of BVDV (referred to as biotypes I and II) based on certain viral RNA sequences in the 5' untranslated region of the genome. Pellerin C, et al., *Virology* 203, 260–268 (1994); J. F. Ridpath et al., *Virology* 205, 66–74 (1994).

BVDV may cause acute infection in cattle, resulting in bovine respiratory disease, diarrhea and severe reproductive losses. Clinical symptoms of acute BVDV infection may range from the almost undetectable to the severe. Infection of pregnant cows and heifers may result in breeding problems (e.g., irregular heats), abortion, premature births or the birth of weak or stunted calves. In some cases, temporary damage to an animal's immune system may occur even when the clinical symptoms are not apparent. In addition to the illness caused by the virus itself, infected animals are more susceptible and are more likely to suffer from other diseases, such as pneumonia.

In addition to causing acute disease, BVDV may also establish persistent infections. Potgieter, *Vet. Clin. North Am. Food Anim. Pract* 11, 501–520 (1995). Persistent BVDV infections are generally established via in utero infection of a developing fetus with a noncytopathic BVDV. The resulting animals are born immunotolerant of the particular BVDV by which they are infected, and may continually shed virus throughout their life span. While some persistently infected animals exhibit congenital malformations due to BVDV infection, many animals persistently infected with BVDV appear clinically normal. Baker, *Rev. Sci. Tech* 9, 25–41 (1990); Bielefeldt-Ohmann, *Vet. Clin. North Am. Food Anim. Pract* 11, 447–476 (1995). Persistently infected animals are thought to be the major disseminators of BVDV in the cattle population.

There are more than 140 vaccines against BVDV commercially available in the United States. Bolin, *Am J. Vet Res.* 46, 2476–2470 (1995). Unfortunately, vaccination does not provide complete protection against BVDV infection, as some vaccinated cattle still become infected with the virus. At present, there is no known cure for BVDV infection. Accordingly, a need exists for an effective treatment for BVDV infection.

In vitro production of embryos has become a useful therapy for increasing reproductive performance of animals and for treating infertility of both animals and humans. In vitro production of bovine embryos could permit the humane, world-wide transfer of genetic material among cattle while limiting the transmission of many pathogens. However, in vitro-produced bovine embryos are potential vectors for transmission of BVDV. B. Avery et al., *Vet Rec* 132, 660 (1993); A. Bielanski et al., *Theriogenology* 46, 1467–1476 (1996); T. Tsuboi et al., *Vet Microbiol* 49, 127–134 (1996); O. Zurovac et al., *Theriogenology* 41, 841–853 (1994). BVDV can be introduced into the embryo production system in association with gametes, serum, somatic cells, cumulus oocyte complexes (COCs), and result in contaminated in vitro fertilized (IVF) embryos or cell lines. K. V. Brock et al., *J Vet Diagn. Invest* 3, 99–100 (1991); C. R. Rossi et al., *Am J Vet Res* 41, 1680–1681 (1980); P. J. Booth et al., *J Reprod Fert Abstr Ser Suppl* 9, 28 (1992); M. D. Fray et al., *Vet Pathol* 35, 253–259 (1998); R. Harasawa et al., *Microbiol Immunol* 39, 979–985 (1995); T. Shin et al., *Theriogenology* 53, 243 (2000). Association of noncytopathic BVDV with transferred IVF embryos may cause infection of embryo recipients, early embryonic death, abortion or birth of persistently infected offspring.

An analogous hazard exists in human in vitro embryo production. Viral transmission to human embryos and embryo recipients by means of contaminated embryo culture media has been reported. Addition of an anti-viral agent to the culture medium surrounding in vitro-produced embryos could prevent or reduce transmission of virus to the embryo or embryo recipient. P. M. Grosheide et al., *Vaccine* 9, 682–687 (1991); W. G. Quint et al., *J Clin Microbiol* 32, 1099–1100 (1994); H. C. van Os et al., *Am J Obstet Gynecol* 165, 152–159 (1991). Accordingly, an antiviral agent that could be added to both animal and human in vitro embryo production systems may have important applications.

The organization of the portion of the BVDV genome that encodes the proteins used in viral replication is very similar to that of human hepatitis C virus (HCV), another flavivirus. S. W. Behrens et al., *J Virol* 72, 2364–2372 (1998). It is believed that more than 80% of the individuals infected with HCV will eventually develop a chronic form of the disease. As the disease develops, the liver of the infected subject is progressively damaged, with the symptoms generally being commensurate with cirrhosis and liver failure (e.g., jaundice, abdominal swelling, and finally, coma). The cycle of disease from infection to significant liver damage can take 20 years or more. Liver failure due to HCV is the presently the leading cause of liver transplants in the United States. It is suspected that there are, at present, more than 5 million people in the United States that are infected with HCV, and perhaps as many as 200 million around the world, making HCV infection a significant public health threat.